COMPUTERS IN PHARMACEUTICAL TECHNOLOGY

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INTRODUCTION

The computer has become a very common tool in all areas of science and technology, and there seems to be no end in sight for future applications. With the proliferation of the Internet and the developments in computer technology and manufacturing, the ratio of price-to-performance of computers continues to decrease. This has resulted in the development of a number of computer applications. The field of pharmaceutical technology has also benefited from the use of computers and will continue to benefit as the professionals in the field gain more familiarity with computers. This chapter will discuss some examples of existing computer applications, the fundamentals of computer technology, and issues to be addressed when applying computers in pharmaceutical technology and assessing their future applications.

COMPUTER APPLICATIONS

Computers have been successfully utilized in pharmaceutical technology to improve productivity, collaborate with other professionals, and to provide solutions for time-consuming manual tasks. For purposes of discussion, the various computer applications are classified as follows:

- Data and information management systems
- Interactive voice response systems
- Group collaboration tools
- Document management and publishing systems
- Internet-based applications and tools
- Problem-solving applications
- Communication aids
- Laboratory automation
- Process control
- Computer-based training

Some computer applications are so complex that it is difficult to classify them into any one of the categories. Nevertheless, any complex computer application can be broken down into smaller parts, and each part may then be described under one of the classifications.

Data and Information Management Systems

The first computers were primarily used for computational purposes. As hardware prices dropped and computer storage technology developed, it became cost-effective to use computers for storing vast amounts of data and information in a variety of formats (e.g., text, numbers, audio, image, and video). Along with the advances in computer hardware, software development also advanced rapidly and resulted in the development of database management packages, such as Oracle, Sybase, and Microsoft Access. By using these packages, a number of computer-based systems can be developed in-house in order to organize data and information and then to query the data in a number of ways. An alternative would be to acquire commercially available systems that use these popular database packages. In either case, the challenge with these systems is to determine what type of information has to be stored in the database and how it can be retrieved in a number of ways. These systems, when designed properly and implemented with active user participation, minimize the paperwork and improve the productivity of personnel involved. Data and information management systems are usually built by the in-house data processing department or acquired from a vendor to meet the needs of users in a given organization. More often than not, the same data management system can be implemented differently in different organizations. A number of systems will be described in general terms in order to give the reader an idea of the available data management programs.

Material inventory system

This system maintains a running inventory of raw materials used in pharmaceutical manufacturing. It will be updated at regular intervals when new materials arrive, as well as when materials are drawn out. This system is useful in tracking existing inventory, lot numbers, and quantities of raw materials needed for manufacturing a product, as well as other pertinent information. Some systems also accommodate the need to reserve a certain lot of raw material for use in manufacturing a particular batch of the product to be used for a stability or clinical study. A sample output from a material inventory system is shown in Fig. 1.

Inventory Report for GMP items

Description	Item #	Unit of measure	Lot #	Quantity
MICROCRYSTALLINE CELLULOSE NF/BP/DAB (AVICEL PH101/EMCOCEL)	Z00106	KGS	SP2359	50.00
MICROCRYSTALLINE CELLULOSE NF/BP/DAB (AVICEL PH102/EMCOCEL 90M)	Z00102	KGS	L00616	10.57
MICROCRYSTALLINE CELLULOSE NF/BP/DAB (AVICEL PH103)	Z00103	KGS	SP1029	9.70
MILLER FROCKS 5 SNAPS L CODE 1212	Z02204	CS	SP2059	1.00
MILLER FROCKS 5 SNAPS M CODE 1212	Z02205	CS	SP2060	1.00
MILLER FROCKS 5 SNAPS S CODE 1212	Z02206	CS	L00604	90.00

Fig. 1 Sample output from a material inventory system.

Formulation information system

This system can be used to store the information on raw materials that constitute a batch of a pharmaceutical bulk product. Typically, the lot numbers of the ingredient, the name of the ingredient, amount per dosage form, percent composition, weight of the batch, and the actual amount of each ingredient are stored in these systems. Other information, such as manufacturing summary, shipping history, and relevant storage information, is also stored. The system's greatest benefit is its different retrieval methods. For example, during product recalls, audits, or tracking an excipient problem, one might be interested in determining all the batches of products made using a particular lot of raw material. This system can also be used to archive the formulation information generated during formulation screening studies. Consequently, data collected in this fashion can be utilized for subsequent statistical analysis. This system can also act as a repository of information that might be helpful in serving as a knowledge base to develop new formulations.

Clinical supplies inventory system

In pharmaceutical research and development (R&D), a number of clinical trials are conducted to determine the therapeutic effectiveness of potential new drugs and novel dosage forms of well-established drugs. In order to provide the necessary clinical supplies in a timely manner and to plan for the manufacture of needed supplies, clinical supplies inventory systems are used.

Clinical supplies labeling

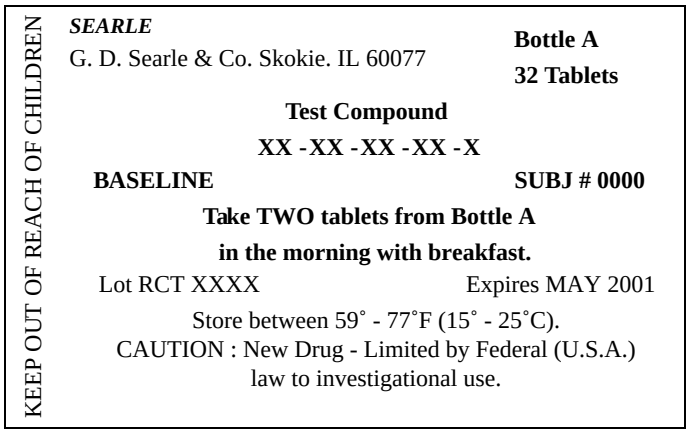
The clinical pharmacy is often called upon to supply complex labeling requirements for investigational drugs used in clinical studies. Depending on the number of patients and investigators, several hundreds or even thousands of labels with randomized patient and investigator numbers are prepared. Well-designed computer programs eliminate the manual labor involved in hand-numbering each label. The computer also sorts the labels by investigators and treatment groups, and prints the labels accordingly. Examples of labels generated by a computer program are shown in Fig. 2.

Stability information systems

The pharmaceutical manufacturer conducts stability studies to develop stable dosage forms in a variety of packages and, in the process, generates vast amounts of data and information. Stability information systems are designed to organize these data and help retrieve the needed information to establish an expiration date for a product. The stability information is also submitted to the regulatory agencies, such as Food and Drug Administration (FDA), from time to time in support of investigational new drug applications (INDAs), new drug applications (NDAs), new dosage forms, abbreviated new drug applications (ANDAs), biological license applications (BLAs), and product license applications. For additional information, the reader is advised to check the following website: http://www.fda.gov/cber/gdlns/stabdft.pdf.

Prior to the start of a stability study, the pharmacist designs protocols, such as the one shown in Fig. 3. When it is time to initiate a study, the computer is used to generate the stability calendar (Fig. 4). Using this calendar and the protocol, the list of samples for chemical, physical observations, and microbiology analysis of a given time period is generated.

The chemical analysis results and the physical observations are stored in a database for further retrieval. The cumulative chemical data are retrieved in the form of tables for inclusion in a regulatory report (Fig. 5) or for review (Fig. 6). The data can also be presented in a graphic form (Fig. 7), which makes it easy to review large amounts



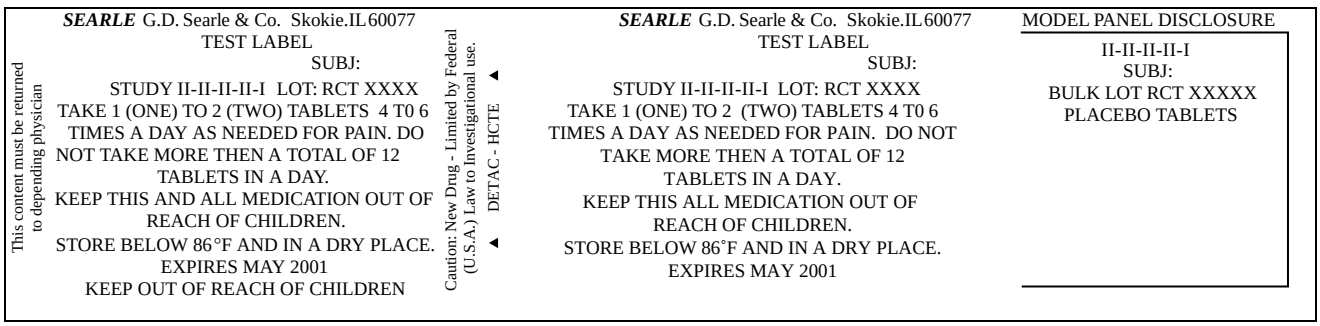


Fig. 2 Sample labels generated by a computer program.

of data in a short time. Other programs that are used to carry out statistical analysis can access the required data from the stability database. The physical observation data are also presented in the form of tables for reporting and review purposes.

Analytical information systems

The analytical laboratory generates vast amounts of data and information while developing analytical methods, supporting product stability studies, and aiding formulation development. The analytical laboratory needs sample management in addition to the management of data it generates. The analytical systems help by providing lists of samples to be analyzed. These are sorted by project, laboratory location, etc. The system also generates reports of analysis (Fig. 8), cumulative analytical data, and other types of reports needed by an organization.

Quality assurance information system

Several systems are used by the quality assurance unit to help carry out quality assurance functions. One such system helps the quality assurance function track information on chemical raw materials, package components, intermediate raw materials, and finished products. The information maintained in this system usually includes a lot number assigned in-house, name of manufacturer, date sampled, and type of release and release status. Using other systems, the quality assurance function compares the physical, chemical, and biological test data generated with the specifications established on products or package components and determines whether the product is released or rejected. Production personnel can access these systems online and determine the status of the materials they have produced or determine the status of raw materials to be used in production. A sample output is shown in Fig. 9.

Interactive Voice Response (IVR) Systems

An IVR system is a specially configured personal computer that contains unique voice software that enables a sound-based interface between a user and the system via a telephone. On the most basic level, these systems let

STABILITY PROTOCOL FOR A TABLET DOSAGE FORM PACKAGED IN ALUMINUM FOIL POUCH
STABILITY NO. : 20000

******* EVALUATION PERIOD - WEEKS *******

STORAGE CONDITION	CODE	0	8	13	26	39	52	78	104	156	208	260
+5 ˚C	C		Ct	Ct	Ct	Ct	Ct	Ct	Ct	Ct	Cn1	Cn1
25˚C-60% RH CL	NH	CP		CP	CP	CP	CP	CP	CP	CP	Cn	Cn
30˚C-60% RH CL	XH			CP	CP	Cn1	CP	Cn				
40˚C-75% RH CL	BH		CP	CP	CP	Cn						

Abbreviations :

P - Physical Tests Ct - Control Sample Cn - Contingency Sample S - Special Instructions

Analytical Tests: E--EXPLORATORY TEST (For Internal Use Only)
C: 3, 10, 11, 17, 22

Compound for Assay: COMPOUND A Impurities or Degradation Products: COMPOUND B

Dissolution : IN GASTRIC FLUID

Physical Tests:

Appearance of tablet and package. Compare to control stored at 5 deg C. Hardness

Instructions:

ICH Study . Stored locally and testing at Contract labs.

Store the following number of samples counted as 1´s : c=100 P=10 Ct=10 Cn=300 Cn1=20

Sample Cn (contingency samples).

A1 pouches are packaged in strips of 2×4´ s for a total of 8 pouches. Each pouch =1´s.

(3). ASSAY (10). DISINTEGRATION (11). DISSOLUTION (17). IMPURITIES OR DEGRADATION PRODUCTS (22). MOISTURE

Fig. 3 A sample stability protocol generated by using a computer program.

callers exchange information with a computer over the telephone without a human intermediary. Popular applications of IVR systems include banking by phone, flight scheduling, and shipment tracking. In the last five years, IVR systems have gained acceptance in the management of clinical trials. Some of the current uses include randomization of patients, drug supply inventory management, real-time patient enrollment status, and emergency code breaking in double blind clinical trials. These systems enable the conduct of clinical trials in multiple countries by providing customized voice prompts in various languages.

STABILITY CALENDAR FOR THE PROTOCOL 20000

NH – 0	10 – DEC – 1999
C – 8 BH – 8	4 – FEB – 2000
C – 13 NH – 13 XH – 13 BH – 13	10 – MAR– 2000
C – 26 NH – 26 XH – 26 BH – 26	9 – JUN – 2000
C – 39 NH – 39 XH – 39 BH – 39	8 – SEP – 2000
C – 52 NH – 52 XH – 52	8 – DEC – 2000
C – 78 NH – 78 XH – 78	8 – JUN – 2001
C – 104 NH – 104	7 – DEC – 2001
C – 156 NH – 156	6 – DEC – 2002
C – 208 NH – 208	5 – DEC – 2003
C – 260 NH – 260	3 – DEC – 2004

Fig. 4 A sample computer-generated stability calendar.

STABILITY DATA TABLE FOR INCLUSION IN A REPORT

STABILITY OF ABC PRODUCT, 100 MG CAPSULES

STABILITY STUDY NUMBER		20000					
PACKAGE DESCRIPTION		ALUMINUM FOIL POUCH, 30 CAPSULES					
IDENTIFICATION CODE		AXY-142-84					
DATE STORED		21-FEB-95					
ASSAY SUBJECT		COMPOUND A	<= = = = = = = DISSOLUTION = = = = = = = =>				
ASSAY METHOD		HPLC, %	UV				
STORAGE CONDITION	EVALUATION PERIOD (WEEKS)		% DISSOLVED Hours				
			1	2	4	5	8
	0	100.4	6.3	13.7	29.2	36.8	58.0
40°C	4	104.1	5.6	11.7	24.0	30.1	47.3
	13	98.9	6.2	12.9	26.4	33.2	51.7
	26	100.1	--	--	--	--	--
	52	99.0	--	--	--	--	--
	104	101.6	--	--	--	--	--
40°C-75% RH OP	4	105.0	6.0	12.4	25.4	31.8	49.5
	13	99.9	6.2	13.1	27.1	34.0	53.1
30°C-60% RH CL	13	99.7	5.6	13.0	28.7	36.3	57.0
	26	99.7	6.7	14.2	29.3	36.7	56.5
	52	99.6	6.2	13.1	27.3	34.2	53.2
	78	100.0	6.3	13.4	28.0	35.3	55.3
	104	100.0	5.2	11.3	24.4	31.0	49.6
	156	105.2	5.3	11.2	23.9	30.4	49.3

Fig. 5 A sample table generated from a stability database for inclusion in a report.

CUMULATIVE ANALYTICAL DATA

Name of Product: ABC PRODUCT 100 MG TABLETS 7-Apr-2000 10:37 AM

CUMULATIVE ASSAY DATA BY STABILITY NO: 20000

COMPOUND	STAB NO	CODE	DATA			AVG	S.D	UNITS	METHOD NO.	ANALYSIS NUMBER
COMPOUND A	20000	A-4	94.8	95.9	96.6	95.8	0.9	#LBL CLM	TAM 30-992306	99-0862
COMPOUND A	20000	A-8	95.4	97.8	95.3	96.2	1.4	#LBL CLM	TAM 30-992306	99-0862
COMPOUND A	20000	A-13	97.9	96.4	97.2	97.2	0.8	#LBL CLM	TAM 30-992306	99-0864
...			...							...
...			...							...
...			...							...

CUMULATIVE IMPURITY DATA BY STABILITY NO: 20000

COMPOUND	LOT	CODE	DATA			AVG	S.D.	UNITS	METHOD NO.	ANALYSIS NUMBER
COMPOUND B	20000	A-4	<0.1	<0.1	<0.1	<0.1		%	TAM 30-892306	99-0862
COMPOUND B	20000	A-8	0.1	0.1	0.1	0.1		%	TAM 30-892306	99-0863
COMPOUND B	20001	A-13	0.1	0.1	0.1	0.1		%	TAM 30-892306	99-0864
...			...							...
...			...							...
...			...							...

The letter A in CODE field refers to storage condition 55˚C

Fig. 6 Cumulative analytical data for review purposes.

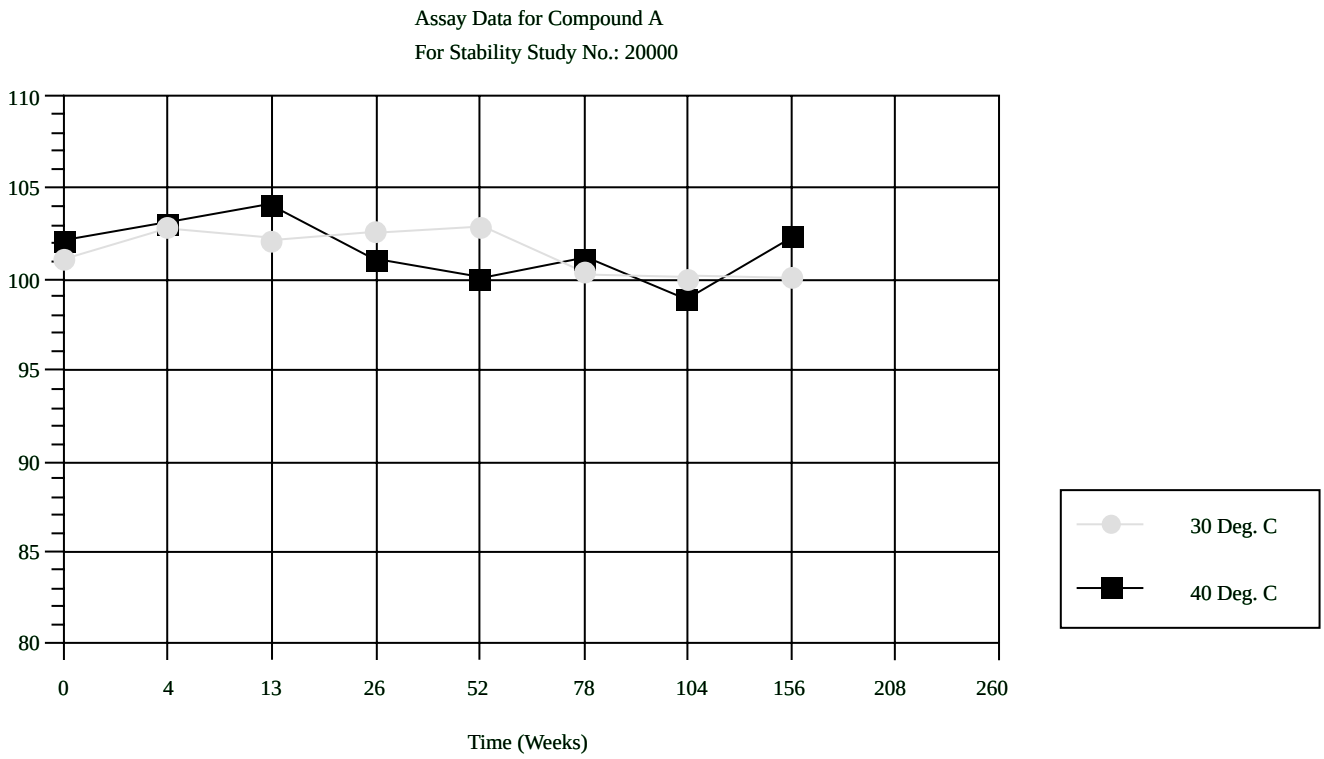


Fig. 7 Graphical representation of cumulative assay data for a stability study.

Group Collaboration Tools

The exponential growth in Internet technologies has allowed companies to set up private Internets, known as Intranets, for effective sharing of information and online meetings where the participants can see each other to collaborate on projects. These tools help to archive project documentation and provide capabilities for searching information across several projects with ease. Some current uses of these tools include collaboration between geographically distributed pharmaceutical R&D and manufacturing plants on process technology data and information.

Document Management and Publishing Systems

In the last 15 years, the size of a typical new drug application has grown from thousands of pages to several hundred thousand pages. To cope with this and to help speed up the submission process, a number of software tools have been developed. These tools provide control and access to documents in a collaborative environment and help publish electronic and paper copies of submissions.

Internet-Based Applications and Tools

Easy navigation of the Internet led to the development of software applications that use web pages for data collection, analysis, browsing, and reporting. As a result, it is becoming easier to deploy software that gathers patient enrollment status information and certain types of clinical trial data. In addition, a number of search tools have been developed that query information across several hundred million pages of information currently available on the Internet. Examples of these tools include Alta Vista, Excite, and HotBot. More information on these tools can be found on www.altavista.com, www.excite.com, and www.hotbox.com.

Project Management Systems

The successful development of a new pharmaceutical product requires careful planning of various activities and resources, as well as tracking the project's progress. A small project is not difficult to monitor manually; however, multiple projects benefit from an automated tool to support the planning process as well as the monitoring of various activities. In addition, these systems will help develop "what if" scenarios for the resources in

REPORT OF ANALYSIS

PRODUCT DEVELOPMENT ANALYTICAL DEPARTMENT

Page: 1
7-Apr-2000

REPORT OF ANALYSIS

Analysis No: 99-2721 Version 1 Group: AN

Material: PLACEBO 50mg FILM-COATED TAB Proj Code: 5811

Lot No. RCT XXXXX
Sample :BEGIN, END

Requested By: C MAH Dept: CLP

Objective: R & D Q.C. RELEASE

Received Date: 17-Dec-1999 Completion Date: 14-Jan-2000

R & D QUALITY CONTROL * G.R. Dill 18-JAN-2000
*

APPROVED

*REEVALUATION DATE: 30-APR-2002

Almedica blister strips

APPEARANCE:

Lot	Sample	Result
RCT XXXXX	BEGIN	WHITE ROUND CONVEX TABLET.
RCT XXXXX	END	WHITE ROUND CONVEX TABLET.

IDENTITY:

Lot	Sample	TEST/COMPOUND	RESULT
RCT XXXXX	BEGIN	UV/AA-66106	TABLET STRENGTH AND UV SPECTRUM CONFORM TO AA -66106 50 mg TABLET.
RCT XXXXX	END	UV/AA-66106	TABLET STRENGTH AND UV SPECTRUM CONFORM TO AA -66106 50 mg TABLET.

COMMENT
STRIP COLOR CODE OF BEGINNING AND END SAMPLES: MAGENTA.

Lot. No. RCT XXXXX Sample : BEGIN, END

TEST	ANALYST	BOOK	PAGE	SUPERVISOR	METHOD NO.
1	L. K. BROADUS	11511	56	G. MADSEN	N99-044-B1099
16	L. K. BROADUS	11511	56	G. MADSEN	N99-044-B1099

Fig. 8 A sample report of analysis.

QUALITY ASSURANCE IN FORMATION

LOT NUMBER	ITEM NUMBER	MATERIAL	VENDOR INFORMATION	SUBMITTER DEPT.	GROUP	DATE RECEIVED	TYPE OF RELEASE	ANALYSIS NUMBER
SP1890	R00106	MICROCRYSTALLINE CELLULOSE NF/BP/DA	FMC 175	K.DUN MMD	* PDAD *MICRO *RDQC	29-Jan-1998	FULL	98-0268
RELEASED ON 27-Mar-1998 Reev. Date: JAN 2000								
SP1890	R00106	MICROCRYSTALLINE CELLULOSE NF/BP/DA	FMC	K.DUN	* RDQC	29-Jan-1998	FULL	NONE
RELEASED FOR EXPLORATORY USE ONLY ON 29 -Jan-1998 Resv. Date: JAN 2000								
SP6846	R00106	MICROCRYSTALLINE CELLULOSE PH101	FMC 1930	K.DUN MMD	PDAD MICRO RDQC	7-Sep-1999	FULL	99-1848
STATUS : PENDING								
SP3591	R00102	MICROCRYSTALLINE CELLULOSE PH102	FMC CORP 2855	A.SUL PDD	* PDAD *MICRO *RDQC	25-Jan-1999	FULL	99-0189
RELEASED ON 23-Feb-1999 Reev. Date: JAN 2001								
SP3591	R00102	MICROCRYSTALLINE CELLULOSE PH102	FMC CORP	A.SUL	* RDQC	27-Jan-1999	FULL	NONE
RELEASED FOR EXPLORATORY USE ONLY ON 21 -Jan-1999 Resv. Date: JAN 2001								

Fig. 9 A sample output from a quality assurance information system.

Table 1 Commercially available statistical software packages

Name	Source
Statistical Analysis System (SAS)	SAS Institute Inc. SAS Campus Drive Cary, NC 27513-2414 Web address: http://www.sas.com/
MINITAB	Minitab Inc. 3081 Enterprise Drive State College PA 16801-3008 Web address: http://www.minitab.com/
WINNONLIN	Pharsight Corporation 800 W. El Camino Real, Suite 200 Mountain View, CA 94040 Web address: http://www.pharsight.com/

the new projects as well as help to terminate the projects. Several project management systems currently available on the market are designed to fulfill these needs. These systems are available for all types of computers—from personal computers to mainframes.

Problem-Solving Applications

The computer is an excellent tool for statistical analysis of data and for solving mathematical problems. Commercial software packages (Table 1) are generally used for statistical analysis. The scientist often works with the statistician to design an experiment and determine the most appropriate statistical method to analyze the collected data. Custom-designed software or commercial software that allows tailoring is generally used to solve mathematical problems.

Spreadsheet Software

This software is available commercially for almost all types of computers and is becoming a valuable tool to solve mathematical problems. The data are entered in the form of tables, the mathematical formulae are defined, and at the push of a button the answer is obtained. The user can easily modify the formula as well as add rows or columns of data and obtain the results easily and quickly. As such, this software enables the user to determine "what-if" scenarios for the problem at hand. It also is extremely valuable in helping the pharmacist compute percent composition and the amount of each ingredient necessary for preparing different strengths of dosage forms. In addition to providing the computational ability, the software also enables the user to prepare data and information in the form of tables and plots.

Expiry Date Prediction

Expiration dating, required on the label of a drug product by good manufacturing practices (GMPs), is arrived at by analysis of data collected on samples exposed to storage conditions defined in a stability protocol. The establishment of an expiry date has evolved from "eyeballing" the time–temperature plot on graph paper and drawing an approximate regression line, to the rigorous application of physical–chemical laws and sophisticated statistical analysis using computers (1). Using the speed and accuracy available from the computer and expert advice from a statistician, the pharmaceutical scientist can try various statistical models to fit the data and arrive at an optimal expiration date.

Pharmacokinetics

For a number of years, computers have been successfully utilized in pharmacokinetics (2) to: 1) fit blood-level data to the appropriate model (single, two, or multiple compartments) and to calculate model parameters, such as absorption rate constant, elimination rate constant, half-life, and volume of distribution (3); 2) evaluate bioavailability parameters, such as peak plasma concentration, time of peak concentrations, and area under the concentration time curve obtainable from a blood-level curve (4); and 3) calculate dosage regimens in patients with renal failure (3).

Currently, the growing trend is to make use of physiologically–based pharmacokinetic models to study the behavior of drugs in animals and extrapolate the data to humans (4, 5). In this context, computers will be of immense help in developing predictive models that might assist in the scale-up of animal data to humans and predicting the concentration of drugs in human body fluids.

Microcomputers are also used to systematize, speed up formulation, simplify manufacturing processes, and reduce the number of needed bioavailability studies through simulated models and plasma level predictions. Commercially available software packages, such as WINNONLIN, SAS (Table 1), and other custom-designed programs, are generally used to solve the often complex mathematical formulae encountered in pharmacokinetic research and applications.

Communication Aids

The computer has become an excellent tool for communication. It can store information entered by one user and send a signal to another user who then reads the information. When several computers are connected through a network, users of one computer can send information to other users in the network almost instantaneously. This feature makes the computer a powerful and effective communication medium for organizations with various remote locations. Examples of communication aids are discussed below.

Electronic mail

With the proliferation of the Internet, electronic mail (e-mail) has become an integral part of browsers, such as Netscape Navigator and Microsoft Internet Explorer. At times, e-mail software is also bundled into other office automation software packages, such as word processing. This e-mail software allows users to send messages to other users (with e-mail accounts) anywhere on the Internet. In addition to sending mail messages to other users, the software allows the user to file, forward, reply, delete, and print messages sent by others. Most e-mail software packages allow attachment of files that contain text, graphics, video, or audio information. Electronic mail provides almost instantaneous communication to remote users, helps improve the productivity of firms operating on a worldwide basis, and improves communication with regulatory agencies.

Distributed information management systems

A pharmaceutical company with different geographic locations often has a need to communicate between locations in order to share data and information. Using the concept of distributed data processing, the company sets up a data processing center at each location and connects these centers by networks. In this setup, common data management systems running at each site make it easy for the company to work on the same project at several sites and funnel the information back and forth. For example, a company conducting toxicology or stability studies can consolidate the information at one site and use it for generating regulatory reports or for other purposes. In addition, these systems help transfer technology developed at one site to another site and allow access to data generated from other sites.

Laboratory Automation

Many laboratory instruments available on the market today contain built-in microprocessors that process data collected on samples and display or send the answer to a computer. In addition, they may have an interface that attaches to an external computer for processing the data generated by the instrument. With regard to experiments or analyses performed frequently, it is often desirable to interface the instrument to a computer to aid in the subsequent analysis of data. Some of the commonly encountered systems following.

Chromatography systems

The computer has become a valuable tool in automating chromatographic techniques, especially high-performance liquid chromatography (HPLC). Prior to automation, strip chart recorders were used to record the analog signals from an HPLC detector, and the calculations were done manually. In automated systems, the output from an HPLC detector is digitized through an analog-to-digital (A/D) converter, the digitized information is stored in the computer, and the data is analyzed to compute the final result. The inherent disadvantages associated with a strip-chart recorder are overcome in automation because the computer enables the analytical chemist to change calculation parameters (e.g., the base line, peak start, and peak end) as needed. As a result, the number of repeat analyses to be performed is minimized. The computer, utilized as a systems controller, is especially useful in applications that require techniques such as column switching and solvent gradients.

Automated dissolution systems

The application of computers to solid dosage form dissolution allows for nearly complete automation. Analyst intervention is limited to the analysis setup. The computer executes all other steps by controlling the system devices, such as the sampling pump and the spectrophotometer generally used for analysis. Typically, a fraction of the sample solution is pumped into a spectrophotometer flow-through cell, where its absorbance is measured. The computer uses the absorbance reading to perform calculations and reports the analysis results in a tabular or graphic format. Sampling, analysis, quantitation, data handling, and reporting are all performed by the computer according to the analysis parameters specified before each run or included in a setup table (6). Automation has played a key role in the development of dissolution systems, which attempt to simulate changes in pH in the gastrointestinal tract or the presence of bile salts (7).

Microprocessor-based balances

Microprocessor-based balances are used in the pharmaceutical industry for automating a number of routine operations. Some organizations use these balances to

automate the United States Pharmacopoeia (USP) weight variation test. In this application, the printer attached to the balance prints a hard copy of the individual weights of the dosage form as well as the average and standard deviation (8). The balances are also used in the toxicology and pathology laboratories to weigh animals or organs and then transmit the information to a central computer for further processing.

Process Control

Computerized process-control systems are used to measure process variables through sensors at predefined intervals, make appropriate decisions, and take appropriate actions to keep the process under control. In an open-loop process-control operation, the computer records sensor readings, compares readings against standards, and notifies human operators of needed actions to regulate devices. In more complex closed-loop process-control operations, the computer records the measurements, makes the comparisons with standards, and transmits signals to the regulating devices to make the necessary changes (9). The automation of process control is often limited by the availability of pharmaceutical processing equipment. To date, a number of companies have succeeded in implementing the process-control applications. Two examples are automated tableting and automated freeze-drying.

Automated tableting

Instrumented tablet presses with computer interfaces allow the pharmaceutical scientist to study the mechanism of compaction and the relationship of the mechanism to tablet-compaction properties and formulations. In addition, automated systems are useful to develop compression profiles for reference purposes, to control weight of tablets during development and production, and to monitor punch wear. This automation reduces the burden on personnel faced with the requirements of quality control (10). Merck Sharp and Dohme's major production facility in the United Kingdom is fully computerized to manufacture a high-volume tablet product as well as multiple-tablet products (11).

Automated freeze-drying

Pharmaceutical or biological products that are unstable in solution form are converted to a stable solid state using the freeze-drying technique and later reconstituted prior to administration to a patient. Freeze-dryer equipment manufacturers are now upgrading their equipment with automated control systems. Typically, the automated control system has a personal computer and a programmable logic controller. The personal computer is used to initiate the process, monitor the process, maintain recipes, and archive data. The programmable logic controller is used to control the freeze-drying, sterilization, and cleaning process by means of instructions downloaded from the personal computer.

The computer is useful in avoiding long freezing times since it is possible to monitor product temperature with ease, and eliminate the need for human operator intervention during transition from one freeze-drying phase to the other. The computer also helps in process documentation and in developing cost-effective freeze-drying profiles that should be useful in scaling up a product from the pilot plant to the production area.

Regulatory Issues Affecting Use of Computers

As previously described, the use of computers and computerized systems in the pharmaceutical industry is growing at a rapid rate. Some of the systems used in the industry range in complexity from the use of personal computers for performing simple tasks (word processing, e-mail, Internet access) to the use of powerful computers in process-control applications. In addition, to help eliminate or reduce paper usage, the pharmaceutical industry has implemented a number of electronic batch record systems in drug substance and product manufacturing to keep track of process documentation.

As the regulatory authority, FDA wants the computerized systems to be validated and requires manufacturers to comply with regulations that cover electronic records and signatures (see http://www.fda.gov/oralcompliance_ref/part). The FDA's *General Principles of Validation Guideline* (12) defines validation as establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. This definition applies to computer systems as well as to the processes. To date, the industry has done a good job in validating computerized systems and is beginning to address the implications of electronic records/signature rule. For additional information on computer systems validation and guidance on electronic records and signatures, visit http://www.pharmaportal.com/articles/pt.fda99.cfm.

Future Trends

The computer provides solutions to problems that can be defined in a language it understands. Although the computer works faster than humans, it still lacks the

human qualities of intuition, insight, and experience. A great deal of effort has been expended in the development of computer languages and software tools that allow for ease in writing programs and obtaining desired solutions. In spite of this, researchers still need programmers to translate their requirements to the computer; it is probably unrealistic at this time to assume that they can do away with programmers. The challenge facing scientists today is to determine ways in which to help nonexperts accomplish sophisticated tasks with computers. In this regard, Internet technologies have helped a great deal by implementing simple-to-use and standardized navigation techniques for accessing and interacting with information on a personal computer. Any savvy Internet user can now buy airline tickets, shop for electronic items, and search the Internet for information on diseases, product specifications, etc. This trend will continue for the foreseeable future.

Human genomics is another area that is beginning to benefit from the use of computers. Researchers have just begun amazing discoveries in this particular field. As more information on the human genome is discovered, we will begin to understand human diseases at a gene level, thus allowing researchers the opportunity to discover cures for deadly diseases.

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